

REMARKS

Claims 1-17 are pending in the instant application. By the above amendments, Claims 5, 7-10, 13 and 15 have been canceled without prejudice, Claims 1-4, 6, 11-12, 14 and 16-17 amended and new Claim 18 added. Support for new claim 18 is found on page 14, lines 11-14 of the specification as filed. After entry of the amendments, Claims 1-4, 6, 11-12, 14 and 16-18 will remain pending and under consideration.

Early favorable action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

Respectfully submitted,

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Version with Markings to Show Changes Made

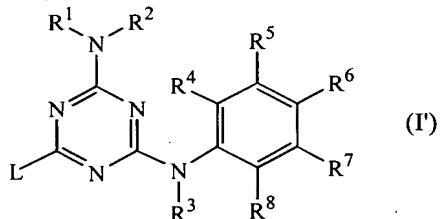
In the Specification:

On page 1, between the Title of the Invention and line 4 of the specification, add the following new paragraph:

This application is a divisional of prior application U.S. Serial No. 09/938,602, filed September 26, 1997, which claims priority from United States provisional application Serial No. 60/027,260, filed October 1, 1996, the contents of which are hereby incorporated by reference.

In the Claims:

1. A compound of formula



a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein
R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁-6alkyl; C₁-6alkyloxy; C₁-6alkylcarbonyl; C₁-6alkyloxycarbonyl; Ar¹; mono- or di(C₁-6alkyl)amino; mono- or di(C₁-6alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁-6alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyC₁-6alkyloxy, carboxyl, mono- or di(C₁-6alkyl)amino, C₁-6alkyloxycarbonyl and thienyl; or
R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁-6alkyl)aminoC₁-6alkylidene;

R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy;

R⁶ is aminocarbonyl; or

L is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; and,

Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl;

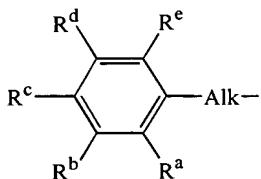
~~with the proviso that the following compounds~~

Ce .N O.	Alk	R ¹ /R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸
a	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	CH ₃	H	H	H	H
b	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NO ₂	H	H
e	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	C ₆ H ₅	H	H	H	H	H
d	1-(4-(2-methylpropyl)phenyl)ethyl	H/H	H	NO ₂	H	CH ₃	H	H

e	\pm (4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	NH ₂	H	H
f	\pm 4-(2-methylpropyl)phenylmethyl	H/H	H	H	CF ₃	H	H	H
g	\pm (4-(2-methylpropyl)phenyl)ethyl	H/H	H	H	H	Cl	H	H
h	\pm 4-(2-methylpropyl)phenylmethyl	H/H	H	H	H	H	H	H
i	\pm 3,4-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
j	\pm 2,3-dimethoxyphenylmethyl	H/H	H	H	H	H	H	H
k	3,4-diethoxyphenylmethyl	H/H	H	H	H	H	H	H
l	\pm 2-(3,5-(1,1-dimethylethyl)-4-hydroxyphenyl)ethyl	H/H	H	H	H	H	H	H
m	\pm 2-(3,5-(1,1-dimethylethyl)-4-hydroxyphenyl)ethyl	H/H	H	H	t-Bu	OH	t-Bu	H
n	phenylmethyl	H/H	H	CH ₃	H	H	H	H
o	phenylmethyl	H/H	H	H	H	H	H	H

are not included.

2. A compound according to claim 1 wherein R¹ and R² are each independently selected from hydrogen, C₁₋₆alkyl, Ar¹ or mono- or di(C₁₋₆alkyl)aminocarbonyl; or R¹ and R² taken together may form pyrrolidinyl, piperidinyl or morpholinyl; R³ is hydrogen, C₁₋₆alkyl or Ar¹; and Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; and L is a radical of formula



wherein Alk is C₁₋₆alkanediyl;

R^a, R^b, R^c, R^d, R^e, R⁴, R⁵, R⁶, R⁷ and R⁸ are each independently selected from hydrogen, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy; or R^a and R^b taken together may form a bivalent radical of formula

-CH=CH-NR⁹- (a-1),

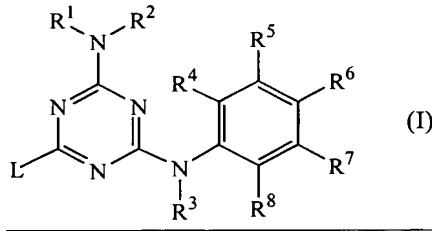
-NR⁹-CH=CH- (a-2),

wherein R⁹ is hydrogen or C₁₋₄alkyl.

3. A compound according to claim ~~1 or 2~~ wherein L is C₃₋₁₀alkenyl or C₁₋₂alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl.
4. A compound according to ~~any one of claims 1 to claim 3~~ wherein L is 2,6-dichlorophenylmethyl.
7. A compound according to claim 4 ~~any one of claims 1 to 5~~ wherein NR¹R² is other than amino.
11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed ~~in any one of claims~~ claim 1 to 7.

12. A process for preparing a pharmaceutical composition as claimed in claim 10 characterized in that comprising intimately mixing a therapeutically effective amount of a compound as claimed in claim 1 any one of claims 1 to 7 is intimately mixed with a pharmaceutically acceptable carrier.

15. The combination of a compound of formula (I)



wherein R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁-6alkyl; C₁-6alkyloxy; C₁-alkylcarbonyl; C₁-6alkyloxycarbonyl; Ar¹; mono- or di(C₁-6alkyl)amino; mono- or di(C₁-6alkyl)aminocarbonyl; dihydro-2 (3H)-furanone; C₁-6alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyC₁-6alkyloxy, carboxyl, mono- or di(C₁-6alkyl)amino, C₁-6alkyloxycarbonyl and thienyl; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁-6alkyl)aminoC₁-alkylidene;

R³ is hydrogen, Ar¹, C₁-6alkylcarbonyl, C₁-6alkyl, C₁-alkyloxycarbonyl, C₁-6alkyl substituted with C₁-alkyloxycarbonyl; and

R⁴, R⁵, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁-6alkyl, C₁-6alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethoxy;

R⁶ is selected from cyano or aminocarbonyl;

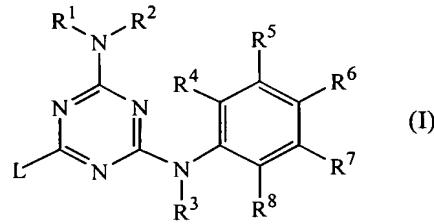
L is C₁-10alkyl; C₃-10alkenyl; C₃-10alkynyl; C₃-7cycloalkyl; or

L is C₁-10alkyl substituted with one or two substituents independently selected from C₃-7cycloalkyl; indolyl or indolyl substituted with one, two, three or four

substituents each independently selected from halo, C₁-alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethoxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethoxy, C₁₋₆alkylcarbonyl; and,

Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl;
as defined in claim 9 and another antiretroviral compound.

16. A product containing (a) a compound of formula (I)



wherein R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy, hydroxyC₁₋₆alkyloxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonyl and thienyl; or R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄alkylidene;
R³ is hydrogen; Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and
R⁴, R⁵, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano,

aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy;

R⁶ is selected from cyano or aminocarbonyl;

L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or

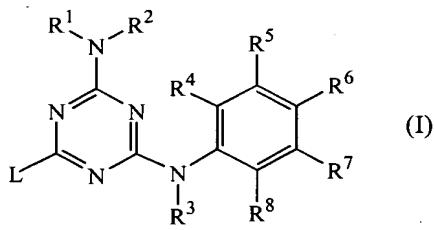
L is C₁₋₁₀alkyl substituted with one or two substituents

independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl;

phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; and,

Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl;
as defined in claim 9, and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound of formula (I)



wherein R¹ and R² are each independently selected from hydrogen; hydroxy; amino; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; Ar¹; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyl)aminocarbonyl; dihydro-2(3H)-furanone; C₁₋₆alkyl substituted with one or two substituents each independently selected from amino, imino, aminocarbonyl, aminocarbonylamino, hydroxy,

hydroxyC₁₋₆alkyloxy, carboxyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonyl and thienyl; or

R¹ and R² taken together may form pyrrolidinyl, piperidinyl, morpholinyl, azido or mono- or di(C₁₋₆alkyl)aminoC₁₋₄alkylidene;

R³ is hydrogen, Ar¹, C₁₋₆alkylcarbonyl, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyl substituted with C₁₋₆alkyloxycarbonyl; and

R⁴, R⁵, R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl or trihalomethyloxy;

R⁶ is selected from cyano or aminocarbonyl;

L is C₁₋₁₀alkyl; C₃₋₁₀alkenyl; C₃₋₁₀alkynyl; C₃₋₇cycloalkyl; or

L is C₁₋₁₀alkyl substituted with one or two substituents independently selected from C₃₋₇cycloalkyl; indolyl or indolyl substituted with one, two, three or four substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, trihalomethyloxy, C₁₋₆alkylcarbonyl; and,

Ar¹ is phenyl, or phenyl substituted with one, two or three substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, cyano, nitro or trifluoromethyl; as defined in claim 9, and (b) another antiretroviral compound.

Add new Claim 18 as follows:

18. A method of treating a subject suffering from HIV (Human Immunodeficiency Virus) infection comprising administering to the subject a therapeutically effective amount of the compound of claim 1.

